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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,154	LANDERS ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11,17-31,35,36,38-41,47-56,140 and 148-166* is/are pending in the application.

4a) Of the above claim(s) *161-164* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,17-31,35,36,38-41,47-56,140,148-160,165 and 166* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04,6/04,9/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Claims 1-5, 8-11, 17-31, 35-36, 38-41, 47-56, 140, 148-160, and 165-166 in the reply filed on 11/13/2006 is acknowledged.

The reply asserts a single search would not place an undue burden on the examiner (p. 1 of response).

These arguments have been fully considered but have not been found persuasive.

The search for each group of invention presents a serious burden as the searches for each group are not coextensive in scope. Art relating to the article of manufacture would not necessarily provide descriptive information for the method of detecting the presence or absence of a SNP allele in a genomic sample.

The requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 1-5, 8-11, 17-36, 38-41, 47-56, 140, 148-166 are pending. Claims 161-164 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. An action on the merits for Claims 1-5, 8-11, 17-31, 35-36, 38-41, 47-56, 140, 148-160, and 165-166 is set forth below.

Information Disclosure Statement

4. The nonpatent literature and the foreign patent documents listed on the IDS forms in the instant case have not been considered. The copies of these references are in the parent case (Patent 6703228). The parent case is in interference and the paper record cannot be obtained by the Examiner at the present time in order to consider the art contained in the record for the IDS in the instant case. It is requested by the examiner that the applicant submit copies of the IDS references so that these references can be added to the record of the current case. All patents listed on the IDS have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17-21, 25, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-21 are indefinite over the phrase "at least a fraction of the SNP-ASO is labeled" in Claim 17. It is unclear if Claim 17 is drawn to one SNP-ASO wherein a portion is labeled or to multiple SNP-ASO wherein some are labeled.

Claim 18 is indefinite. Claim 18 recites the limitation "the non-labeled oligonucleotide" in line 2. There is insufficient antecedent basis for this limitation in the

claim. It is suggested that the claim be amended to correct antecedent basis. It is suggested that the claim be amended to e.g. "the non-labeled SNP-ASO".

Claims 19-20 are indefinite. Claim 19 recites the limitation "the oligonucleotide" in line 2-3. There is insufficient antecedent basis for this limitation in the claim. It is unclear if "the oligonucleotide" is drawn to the labeled SNP-ASO, the RCG , or another oligonucleotide. It is suggested that the claim be amended to correct the antecedent basis.

Claim 25 cites the limitation "the radioactively labeled hybridization products" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to correct antecedent basis.

Claim 27 cites the limitation "the fluorescently labeled hybridization products" in line 2-3. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to correct antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 5, 8, 17-27, 38-39, 47-49, 51-52, and 54-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber et al. (US Patent 5589330 December 31, 1996).

With regard to Claim 1, Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

With regard to Claim 2, Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47). Shuber et al. teaches method of detecting the hybridization of the ASO with the RCG wherein the detection of the hybridization indicates if there is a mutation (characterize the genomic sample) (Column 6 lines 5-10 and column 7 lines 25-35).

With regard to Claim 3, Shuber et al. teaches that the RCG is bound to a solid phase matrix (e.g. immobilized on a surface) (Column 4 lines 21-25).

With regard to Claim 5, Shuber et al. teaches that an ASO probe is individually hybridized with a plurality of RCGs (panel of different patient samples) (plurality of RCGs hybridized with pools of ASOs) (Figure 4).

With regard to Claim 8, Shuber et al. teaches a method of detecting disease causing microorganisms (abstract), therefore Shuber et al. teaches identifying a genotypes (the genotype is the presence or absence of a particular allele associated with a disease).

With regard to Claim 17, Shuber et al. teaches a method wherein the ASOs are labeled (at least a fraction is labeled) (Column 4 lines 50-55).

With regard to Claim 18, Shuber et al. teaches a method in which oligonucleotides contain the nonvariant (complementary to the wild type, a different allele) are added to the hybridization solution to reduce background (Column 5, lines 55-60). The oligonucleotide complementary to the wild type would not be detected and therefore would not be labeled.

With regard to Claim 19, Shuber et al. teaches that RCG are hybridized with labeled ASOs (Column 6 lines 5-10). Shuber et al. teaches RCG (the oligonucleotide) which are complementary to a different allele (Figure 2A). Figure 2A of Shuber et al. shows multiple RCGs performed in parallel on the same matrix. The RCG hybridizes with the ASO but some do not hybridize indicating that there are complementary to a different allele than the mutant allele of the ASO probe.

With regard to Claim 20, Shuber et al. teaches that a pool of ASOs can be used and labeled (Column 4 lines 45-55).

With regard to Claim 21, Shuber et al. teaches a method in which oligonucleotides containing the nonvariant (complementary to the wild type, a different allele) are added to the hybridization solution to reduce background (Column 5, lines 55-60). Therefore Shuber et al. teaches an "excess" of non-labeled ASO probes.

With regard to Claims 22-23, Shuber et al. teaches a method in which the ASO probes can be from 16-25 nucleotides in length (about 10 to about 50 and about 10 to about 25) (Column 4 lines 49-50).

With regard to Claim 24, Shuber et al. teaches a method wherein the probes are labeled with a radioactive isotope (Column 4 lines 54-55).

With regard to Claim 25, Shuber et al teaches a method wherein the RCG is detected on x-ray film (Column 6 lines 13).

With regard to Claim 26, Shuber et al. teaches a method wherein the probe is labeled with flurochromes (florescent molecules) (Column 4 lines 56-57).

With regard to Claim 27, Shuber et al. teaches a method wherein RCG is detected by exciting the fluorescent label and detecting a specific absorption wavelength of the fluorescent reporter (generating an output signal) (Column 6 lines 13-16).

With regard to Claims 38-39, Shuber et al. teaches a method wherein parts of the ASO probe is sequenced to produce characteristic patterns (bar codes) (Column 7 lines 7-15). Therefore, Shuber et al. provides a method wherein the presence of an allele (the hybridization of the ASO to the RCG) determines which ASO probes are present in

the RCG and then these ASO probes are classified based on their sequence into a bar code (a genomic pattern which is a classification code).

With regard to Claim 47, Shuber et al. provides a method wherein the presence of an allele (the hybridization of the ASO to the RCG) generates which ASO probes are present in the RCG and then these ASO probes are classified based on their sequence into a bar code (a genomic pattern which is a classification code) (Column 7 lines 7-15).

With regard to Claim 48, Shuber et al. teaches a method in which the RCG is hybridized with various SNP-ASOs (a panel) wherein the ability of the RCG to hybridize indicates if the RCG has a specific allele and therefore a genomic pattern (See Figure 2A-2D).

With regard to Claim 49, Shuber et al. teaches a method wherein parts of the ASO probe is sequences to produce characteristic patterns (bar codes) (Column 7 lines 7-15). Therefore Shuber et al. teaches that a genomic pattern is generated from the hybridized ASO probes in which there is a characteristic pattern (genomic classification code).

With regard to Claims 51-52, Shuber et al. teaches that the characteristic patterns were analyzed on an automatic sequencer, which would produce a visual pattern (bands) and a digital pattern (data output by the software analysis) (Figure 4).

With regard to Claim 54, Shuber et al. teaches that RCG are hybridized with labeled ASOs (Column 6 lines 5-10). Shuber et al. teaches RCG (the oligonucleotide) is complementary to a different allele (Figure 2A). Figure 2A of Shuber et al. shows

multiple RCGs performed in parallel on the same matrix. The RCG hybridizes with the ASO but some do not hybridize indicating that there are complementary to a different allele than the mutant allele of the ASO probe.

With regard to Claim 55, Shuber et al. teaches the RCG is immobilized on a surface (membrane) and each SNP-ASO is hybridized to a separate surface (figure 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4, 36, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (Column 11 lines 25-30). Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47).

Shuber et al. provides a method wherein the presence of an allele (the hybridization of the ASO to the RCG) generates which ASO probes are present in the RCG and then these ASO probes are classified based on their sequence into a bar code (a genomic pattern which is a classification code) (Column 7 lines 7-15).

However, Shuber et al. does not teach immobilizing the SNP-ASO to the surface.

With regard to Claims 4, 36, and 53, Saiki et al. teaches an nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to immobilize the ASO probes onto a solid support as taught by Saiki et al. The ordinary artisans would have been motivated to modify the teaching of Shuber et al. to immobilize the ASO probes onto a solid support as taught by Saiki et al. because Saiki et al. teaches the preparation of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). The ordinary artisan would be motivated to have immobilized probes on the support in order to be able to test different samples quickly.

9. Claims 9-11, 40, 140 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting

the presence or absence of the allele (Column 11 lines 25-30). Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47).

However Shuber et al. does not teaches a method wherein the genomic sample is obtained from a tumor.

With regard to Claim 9, Hoffman et al. teaches a method of using ASO probes to detect a single base change correlated with breast cancer (tumor) (Abstract). With regard to Claim 10, Hoffman teaches a plurality of patients had genomic DNA isolated (plurality of RCGs) to detect the SNP ((p. 141 1st column last paragraph and 2nd column ASO hybridization). With regard to Claim 11, Hoffman et al. teaches detection of the SNP in genomic DNA collected from members of Family 53 with breast cancer and DNA from individuals without breast cancer (random selection from the population of family 53) (p. 141 1st column last paragraph). Hoffman et al. teaches the presence or absence of the SNP allele of each patient and the number of total genomic patient samples (Table 1 and p. 141 last full paragraph), therefore Hoffman et al. teaches the allelic frequency.

With regard to Claim 40, Hoffman et al. teaches preparing RCGs form genomic DNA (p. 141 1st column last paragraph and 2nd column ASO hybridization). Hoffman et al. teaches hybridization of the ASO with the RCG (p. 141 2nd column ASO hybridization). Hoffman et al. teaches that the ASO binds to the variant or the complimentary normal (complementary to one allele). Hoffman et al. teaches detection of cancer (tumor) in genomic samples (Table 1).

With regard to Claim 140, Hoffman et al. teaches preparing the RCG and assessing subjects in a family for the presence or absence of a wild type snp allele and a mutant SNP allele (p. 141, table 1, and Figure 2). Hoffman et al. teaches that at least 10% of the individuals in the family hybridized with the mutant probe (6 members) (Figure 2). These 6 members were associated with members of the family associated with cancer (disease) (Table 1).

With regard to Claim 148, Hoffman et al. teaches a method prepares individual RCGs from members of Family 53 (p. 141 1st column last paragraph). Hoffman et al. teaches determining the presence or absence of SNP alleles in the RCGs (p. 141 2nd column ASO). Hoffman et al. teaches comparing the RCGs of the family members (Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to detect a SNP associated with breast cancer (tumor) in a given population to determine the allelic frequency as taught by Hoffman et al. The ordinary artisans would have been motivated with a reasonable expectation of success to modify the teaching of Shuber et al. to detect a SNP associated with breast cancer as taught by Hoffman et al. because Hoffman et al. teaches that a population can be screened quickly for mutation status to facilitate early diagnosis and treatment (p. 140 2nd column 2nd full paragraph). The ordinary artisan would have been motivated to screen a given population for a SNP associated with tumor in order to quickly screen patients for a particular mutation and treat cancer at an earlier stage.

10. Claims 28-30 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Drmanac et al. (US Patent 6383742 May 7, 2002).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (Column 11 lines 25-30).

Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47). Shuber et al. teaches that a pool of ASOs can be used and labeled (Column 4 lines 45-55). Shuber et al. teaches a method wherein the probe is labeled with flurochromes (florescent molecules) (Column 4 lines 56-57).

Shuber et al. provides a method wherein the presence of an allele (the hybridization of the ASO to the RCG) generates which ASO probes are present in the RCG and then these ASO probes are classified based on their sequence into a bar code (a genomic pattern which is a classification code) (Column 7 lines 7-15).

However Shuber et al. does not teach a method wherein each SNP-ASO is labeled with a distinct fluorescent.

Drmanac et al. teaches a method of detection of a target nucleic acid species where there is a plurality of labeled probes (Abstract). With regard to Claims 28-30 and 56, Drmanac et al. that in a mutation screening procedure, "two to sex probes, each having a different label such as a different florescent dye, may be used as a pool, thereby reducing the number of hybridization cycles and shortening the sequencing process". (Column 8 lines 9-12).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to incorporate the individual detection of each of the probes in the pool of probes by detection of distinct florescent molecules as taught by Drmanac et al. The ordinary artisans would have been motivated with a reasonable expectation of success to modify the teaching of Shuber et al. to incorporate the individual detection of each of the probes in the pool of probes by detection of distinct florescent molecules as taught by Drmanac et al. because Drmanac et al. teaches a method of labeling multiple probes in order to reduce the number of hybridization cycles needed to sequence a mutation thereby shortening the sequencing process (Column 8 lines 9-12)

11. Claims 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of in view of

Drmanac et al. (US Patent 6383742 May 7, 2002) as applied to Claims 28-30 above and in further view of Manos et al. (US Patent 5182377 January 26, 1993).

Neither Shuber et al. nor Drmanac teach labeling the RCGs.

It is well known in the art that either the probe or the target (RCG) may be labeled for detection.

With regard to Claims 31 and 35, Manos et al. teaches a detection method wherein either the target (RCG) or the probe can be labeled (Column 8 lines 44-45).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. and Drmanac et al. to incorporate a plurality of labeled RCGs. The ordinary artisan would have been motivated with a reasonable expectation of success to modify the teaching of Shuber et al. and Drmanac et al. to incorporated a plurality of labeled RCGs, because Manos et al. teaches that hybridization between a target (RCG) and a probe works equally well when either the RCG or the probe is labeled (Column 8 lines 44-45). The ordinary artisan would be motivated to label the RCG so that multiple hybridization reactions could be performed without labeling each individual probe set.

12. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140) as applied to Claims 9-11 and 40 above and further in view of Saiki et al. (WO 89/11548 November 30, 1989).

Though Shuber et al. and Hoffman et al. teach a hybridization method wherein RCG are hybridized and individually analyzed (Table 1 of Hoffman et al.), Shuber et al. and Hoffman et al. do not teach a method of attaching ASO to a solid support.

With regard to Claim 41, Saiki et al. teaches an nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. and Hoffman et al. to immobilize the ASO probes onto a solid support as taught by Saiki et al. The ordinary artisan would have been motivated to modify the teaching of Shuber et al. and Hoffman et al. to immobilize the ASO probes onto a solid support as taught by Saiki et al. because Saiki et al. teaches the preparation of immobilized probes can separate in time from their use allowing for storage of the support to be used to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). The ordinary artisan would be motivated to have immobilized probes on the support in order to be able to test different samples quickly.

13. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which

genomic DNA (native DNA) is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (Column 11 lines 25-30).

Shuber et al. provides a method wherein the presence of an allele (the hybridization of the ASO to the RCG) generates which ASO probes are present in the RCG and then these ASO probes are classified based on their sequence into a bar code (a genomic pattern which is a classification code) (Column 7 lines 7-15).

However, Shuber et al. does not specifically teach that the genomic pattern is generated using the allelic frequency of the SNPs.

Shuber et al. does teach a method of screening mutations and of determining which alleles are present in a particular sample. Therefore it would be prima facie obvious to take the method of Shuber et al. and modify the teaching so that a frequency could be determine between which samples had a particular allele and which samples did not. The ordinary artisan would be motivated to determine in a population the percent, which had a particular SNP in order to determine if a population had a particular mutation.

14. Claims 149-153 and 155-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) as applied to Claims 4 and 36 above and further in view Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676)

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

However, neither Shuber et al. nor Saiki et al. teaches a method using randomly primed PCR to produce the RCG.

With regard to Claim 149, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome with at least one primer. Cheung et al. teaches the amplified fragments of DNA (RCG) are about 500 bp in length (p. 14676 2nd column 1st paragraph), therefore this

fragment would contain less than 20% of the genomic material present in the whole genome.

With regard to Claims 150-152, Cheung et al. teaches that the RCG would be about 500 bp in length (p. 14676 2nd column 1st paragraph). The human genome is about 3 X 10^9 bp in length (p. 14676 2nd column 1st paragraph). Therefore the 500 bp RCG would represent less than 0.05% of the whole genome.

With regard to Claim 153, Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification).

Shuber et al. teaches using ASO probes to detect the presence or absence of an allele. Therefore Shuber et al. teaches using SNP ASOs wherein 50% of the time they are in the RCG (the allele is present). With regard to Claims 155-156, Shuber et al. teaches a method in which the ASO probes can be from 16-25 nucleotides in length (about 10 to about 50 and about 10 to about 25) (Column 4 lines 49-50).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. The ordinary artisan would have been motivated to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. because Cheung et al. teaches this method offers a way to amplify small genomic DNA samples to allow hundreds-fold more DNA for genetic analyses (p. 14676 2nd column 1st paragraph last sentence). The ordinary artisan would be motivated to use the DOP

method as taught by Cheung et al. to produce RCGs because Cheung et al. teaches that one can completely cover the entire human genome by breaking up the genome into discrete fragments (Abstract). Cheung et al. further teaches that using the DOP PCR method a small biopsy sample can be used to generate sufficient material for many hundreds of genotyping (p. 146749 1st column last paragraph). Therefore the ordinary artisan would be motivated to produce a large number of RCGs so that many different ASO-probes could be tested in order to diagnose various diseases.

15. Claims 157- 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140) as applied to Claims 41 above and further in view Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

Hoffman et al. teaches a method of detecting genetic alterations in DNA in tumor samples (cancer patients) (Abstract).

However, neither Shuber et al. nor Saiki et al. teaches a method using randomly primed PCR to produce the RCG.

With regard to Claim 157, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome with at least one primer. Cheung et al. teaches the amplified fragments of DNA (RCG) are about 500 bp in length (p. 14676 2nd column 1st paragraph), therefore this fragment would contain less than 20% of the genomic material present in the whole genome.

With regard to Claims 158, Cheung et al. teaches that the RCG would be about 500 bp in length (p. 14676 2nd column 1st paragraph). The human genome is about 3 X 10^9 bp in length (p. 14676 2nd column 1st paragraph). Therefore the 500 bp RCG would represent less than 5% of the whole genome.

With regard to Claim 159, Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of detection of SNPs in a

tumor sample using ASO-probes attached to a solid support as taught by the combination of Shuber et al. and Saiki et al. and Hoffman et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. The ordinary artisan would have been motivated to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. because Cheung et al. teaches this method offers a way to amplify small genomic DNA samples to allow hundreds-fold more DNA for genetic analyses (p. 14676 2nd column 1st paragraph last sentence). The ordinary artisan would be motivated to use the DOP method as taught by Cheung et al. to produce RCGs because Cheung et al. teaches that one can completely cover the entire human genome by breaking up the genome into discrete fragments (Abstract). Cheung et al. further teaches that using the DOP PCR method a small biopsy sample can be used to generate sufficient material for many hundreds of genotyping (p. 146749 1st column last paragraph). Therefore the ordinary artisan would be motivated to produce a large number of RCGs so that many different ASO-probes could be tested in order to diagnose various diseases, such as tumors, using a small amount of tissue sample.

16. Claims 165 and 166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). With regard to Claim 165, Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30). Shuber et al. teaches hybridizing the RCG with ASO probes (oligonucleotides) to detect allelic associations (Column 11, lines 25-30). With regard to claim 166, Shuber et al. teaches a method to determine which individuals has a particular variant sequence (abstract), therefore, Shuber et al. teaches a method to determine a genotype of an individual.

However, Shuber et al. does not teach preparing the PCR amplified RCG using randomly primed PCR.

With regard to Claim 165, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of detection of SNPs using ASO-probes as taught by Shuber et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. The ordinary artisan

would have been motivated to modify the method of Shuber et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. because Cheung et al. teaches this method offers a way to amplify small genomic DNA samples to allow hundreds-fold more DNA for genetic analyses (p. 14676 2nd column 1st paragraph last sentence). The ordinary artisan would be motivated to use the DOP method as taught by Cheung et al. to produce RCGs because Cheung et al. teaches that one can completely cover the entire human genome by breaking up the genome into discrete fragments (Abstract). Cheung et al. further teaches that using the DOP PCR method a small biopsy sample can be used to generate sufficient material for many hundreds of genotyping (p. 146749 1st column last paragraph). Therefore the ordinary artisan would be motivated to produce a large number of RCGs so that many different ASO-probes could be tested in order to diagnose various diseases, such as tumors, using a small amount of tissue sample.

17. Claims 149 and 154-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) as applied to Claims 4, 36, and 53 above and further in view Drmanac et al. (US Patent 6297006 October 2, 2001).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20).

Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

However, neither Shuber et al. nor Saiki et al. teaches a method using randomly primed PCR to produce the RCG.

With regard to Claims 149 and 154, Drmanac et al. teaches a method to reduce a gene or genome into fragments (column 50 lines 58-61). Drmanac et al. teaches producing genomic fragments (RCGs) by digesting a gene with restriction enzymes and performing a PCR with a small set of DNA adapters (adapter primer) (column 50 lines 60-66 and Column 51 1-11). It would be obvious that a PCR method would break fragments of DNA into stretches of nucleotides, which represented least than 20% of the genomic material because each RCG fragment would be only a few KB in size.

Shuber et al. teaches using ASO probes to detect the presence or absence of an allele. Therefore Shuber et al. teaches using SNP ASOs wherein 50% of the time they are in the RCG (the allele is present). With regard to Claims 155-156, Shuber et al. teaches a method in which the ASO probes can be from 16-25 nucleotides in length (about 10 to about 50 and about 10 to about 25) (Column 4 lines 49-50).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using adapter PCR as taught by Drmanac et al. The ordinary artisan would have been motivated to modify the method of Shuber et al. and

Saiki et al. to produce the RCG fragments using adapter PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. because Drmanac et al. teaches that by using a small number of adapters a million different fragments may be specifically amplified in identical conditions (Column 51 lines 9-11). The ordinary artisan would be motivated to produce RCGs with adapter PCR, because Drmanac et al teaches that DNA differences between several patients can be analyzed and that this approach eliminates the need for expensive genetic mapping on extensive pedigrees (Column 51 lines 13-23). The ordinary artisan, therefore, would be able to detect genetic differences between subjects quickly and with less cost.

18. **Claims 157 and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140) as applied to Claims 41 above and further in view Drmanac et al. (US Patent 6297006 October 2, 2001).**

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

Hoffman et al. teaches a method of detecting genetic alterations in DNA in tumor samples (cancer patients) (Abstract).

However, neither Shuber et al. nor Saiki et al. teaches a method using randomly primed PCR to produce the RCG.

With regard to Claims 157 and 160, Drmanac et al. teaches a method to reduce a gene or genome into fragments (column 50 lines 58-61). Drmanac et al. teaches producing genomic fragments (RCGs) by digesting a gene with restriction enzymes and performing a PCR with a small set of DNA adapters (adapter primer) (column 50 lines 60-66 and Column 51 1-11). It would be obvious that a PCR method would break fragments of DNA into stretches of nucleotides, which represented least than 20% of the genomic material because each RCG fragment would be only a few KB in size.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of detection of SNPs in a tumor sample using ASO-probes attached to a solid support as taught by the combination of Shuber et al. and Saiki et al. and Hoffman et al. to produce the RCG fragments using Adapter PCR as taught by Drmanac et al. The ordinary artisan would have been motivated to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using adapter-PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. because Drmanac et al. teaches that by using a small number of adapters a million different fragments may be specifically amplified in identical

conditions (Column 51 lines 9-11). The ordinary artisan would be motivated to produce RCGs with adapter PCR, because Drmanac et al teaches that DNA differences between several patients can be analyzed and that this approach eliminates the need for expensive genetic mapping on extensive pedigrees (Column 51 lines 13-23). The ordinary artisan, therefore, would be able to detect genetic differences between subjects quickly and with less cost.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1-5, 8-11, 17-31; 35-36, 38-41, 47-56, 148, 165-166 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6703228. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant Claims 1, 165, and 166 contains the same method steps as Claim 1 in Patent No. 6703228 ('228), except that in the instant claim one the RCG is "native RCG" whereas in '228 the RCG is a "randomly primed PCR-derived RCG". The term "native RCG" has not been defined in the instant specification. Therefore, interpreted broadly "randomly primed PCR-derived RCG" would be considered a "native RCG" because the original RCG product is coming from a genomic sample.

Claims 2-5 of the instant application are identical to Claims 2-4 and 6 of '228. Claim 8 of the instant application is identical in scope to Claim 25 of '228. Claims 9-11 of the instant application are identical to Claims 26-27 of '228. Claim 17-21 of the instant application are identical to Claims 7-11 of '228. Claims 22-23 of the instant application are identical to Claims 20-21 of '228. Claims 24-31 and 35 of the instant application are identical to Claims 12-19 of '228. Claim 36 of the instant application is identical to claim 5 of '228. Claim 38-39 of the instant application are identical to claims 23-24 of '228.

Claim 40 of the instant application is obvious over Claims 1, 9, and 27 of '228.

Claim 41 of the instant application is obvious over Claim 19 of '228. Claim 41 is drawn to analyzing RCG separately. Claim 19 of '228 is drawn to labeling each of the

RCGs with a separate and distinct fluorescent molecule. It is obvious that if each RCG is distinct that it would be analyzed separately.

Claims 47-50 of the instant application are obvious over Claims 23-24 and 26 of '228.

Claims 51-52 of the instant application are obvious over Claims 26 and 15 of '228. It is obvious that if the RCG is measure by a fluorescence reader to generate an output signal that the reading would be visual and digital.

Claim 53-56 of the instant application are obvious over Claims 3, 9, 14, and 23 of '228.

Claim 148 of the instant application is obvious over Claim 26 of '228. A population would include a "family".

Conclusion

21. No Claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER